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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,020	GISH ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2003 and 25 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-44* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-6 and 8-44* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply.*

DETAILED ACTION

1. The amendment filed November 9, 2001 is acknowledged but the requested amendment to the specification has not been entered in full. Applicant has requested replacement of Table 2 beginning at page 96, line 5 of the specification with the substitute at page 3 of the amendment; but because Table 2 begins at page 109, rather than at page 96 the replacement has not been made.

2. The response filed April 11, 2003 is acknowledged and have been entered. Claim 7 has been canceled. Claims 32-44 have been added.

3. The response filed August 25, 2003 is acknowledged and has been entered.

4. Claims 1-6 and 8-44 are pending in the application. Claims 1-6 and 8-31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed April 11, 2003.

5. Claims 32-44 are currently under prosecution.

Lack of Compliance under 37 CFR §§ 1.821-1.825

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. As set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, because the amendment filed November 9, 2001 was not entered in full, the sequences disclosed at pages 109-111 are not properly identified by a sequence identification number corresponding to the same sequence set forth in the sequence listing. Applicant must comply with the requirements of the sequence rules

(37 CFR §§ 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

Applicant is given the same period of time within which to reply to this Office action to correct the deficiency so as to comply with the sequence rules (37 CFR §§ 1.821 - 1.825) in order to avoid abandonment of the application under 37 CFR § 1.821(g).

Election/Restrictions

7. In the response filed April 11, 2003 Applicant elected "with traverse the group comprising claim 7" (Response, page 3), re-written as claims 32-44, drawn to a method for diagnosing colorectal cancer comprising determining the expression of a gene, which is at least 90% identical to SEQ ID NO: 1. Accordingly, because claim 7 was re-written as claim 32, and claim 32 is drawn to a single sequence, Applicant has argued in the paper filed August 25, 2003 that the response filed April 11, 2003 was fully responsive to the Office action mailed February 11, 2003.

Therefore, in the interest of advancing prosecution, the responses filed April 11, 2003 and August 25, 2003 have been construed as an election with traverse of claim 7, wherein said method comprises determining the expression of a gene, wherein said gene is SEQ ID NO: 1. As claim 7 has been canceled and claims 32-44 are presently drawn to the elected invention, claims 32-44 are currently under prosecution; and claims 1-6 and 8-31 have been withdrawn from further consideration, as being drawn to non-elected inventions.

Applicant's traversal of the restriction set forth in the response filed April 11, 2003 is acknowledged. Applicant has argued that the restriction is improper because the Examiner has not established that examining more than one group would be a serious burden and because searching one group will identify art pertaining to the others. Applicant's arguments have been carefully considered but not found persuasive. The reasons restriction for examination purposes as indicated in the Office action mailed February 11, 2003 is proper, were set forth therein. Because these inventions are distinct for the reasons given and also because the search required for any one group is

not required for any other group and/or the inventions have acquired a separate status in the art as shown by their different classification or their recognized divergent subject matter, the restriction is deemed proper. Moreover, in answer to Applicant's argument searching one group will identify art pertaining to the others, the search required to examine any one invention is not co-extensive with the search required to search any other; different searches would need be performed to examine each group and such need would constitute serious burden.

The restriction and election requirement is made FINAL.

Specification

8. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion. See pages 11, 15, and 16 for examples of recitations, which make such references.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference.

9. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include Genbank™ (page 11), Teflon™ (page 50), and Trizol™ (page 60).

Appropriate corrections are required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate

symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

10. The specification is objected to because of the following informalities:

(a) The term "ºC" is mistyped as "oC" at, for example, page 61;

(b) The term "µl" is mistyped as "ul" at, for example, page 63; and

(c) The chemical formula "H_2O" is mistyped as "H2O" at page 64.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claims 32-44 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 32-44 are drawn to a method comprising determining and comparing the levels of expression of a gene, which is at least 90% identical to SEQ ID NO: 1, in a first sample acquired from a first individual and a second sample acquired from a second, unaffected individual, wherein a difference in the levels of expression of the gene indicates the first individual has colorectal cancer.

The specification asserts the claimed invention is useful as a means of diagnosing colorectal cancer.

The instant application provides a description of a polynucleotide sequence, namely SEQ ID NO: 1, which appears to be the sequence of the "CBF9 gene". The table at page 109 appears to list the Genbank™ accession number of the sequence set forth therein; however, it is duly noted Genbank™ Accession No. AC005383 differs markedly from the sequence set forth in Table 2. Genbank™ Accession No. AC005383

is the 1,217,714 residue polynucleotide sequence of a cloned fragment of human chromosome 10, whereas SEQ ID NO: 1 is only 3,375 nucleotides in length.

At page 6, paragraph 25, the specification discloses the sequences identified in Table 1 at pages 68-108, "exhibit increased expression in colorectal cancer samples" and Table 2 provides the sequence of the "CBF9 gene". However, it does not appear that the Unigene accession number "Hs.157601" by which the "CBF9 gene" is apparently identified, according to Table 2, is recited in Table 1; therefore, it does not appear that the specification teaches whether or not the "CBF9 gene" exhibits increased expression in colorectal cancer samples.

At page 68, paragraph 274, the specification discloses the results show the expression of each of the "genes" listed in Table I is up-regulated in colorectal tumors of various stages; however, the specification does not disclose the stages of the tumors, so it cannot be determined which genes are up-regulated at which stages. For each different nucleic acid molecule tabulated, Table I reports the numeric value of the "Ratio TumMet/Body"; however, the means for deriving the value of this ratio is not disclosed in the specification and moreover the term "Ratio TumMet/Body" is not defined. It cannot be ascertained whether ratio reflects the differential expression of the "gene" relative to a normal colon or rectal tissue specimen, or relative to the average levels of expression of the "gene" in different a variety of different tissues. It cannot be ascertained whether the normal tissue sample, which has been used as a standard for the comparison, was acquired from the same individual from which the tumor specimen was acquired, or from a different individual. It cannot be ascertained whether the normal specimen was of the same tissue type as the tumor specimen (e.g., colon or rectal tissue). Furthermore, it is unclear whether one tumor specimen or multiple tumor specimens were analyzed or whether one normal specimen or multiple normal specimens were analyzed for comparison. As such, one skilled in the art would only be able to guess the derivation of the values of the ratios tabulated in Table 1 and the significance thereof. Therefore, even should Unigene accession number "Hs.157601" or the "CBF9 gene" be listed in Table 1, it would not be understood whether the nucleic

acid molecule of SEQ ID NO: 1 is differentially expressed, and to what extent, in ovarian cancer cells, and at which stages, relative to normal ovarian cells.

With further regard to the data disclosed in Table 1, the specification teaches the tabulated "genes", which are up-regulated in colorectal tumors, are "expressed at a limited fashion or not at all" (page 68, paragraph 274) in at least 28 tissue types. Again, because it does not appear that SEQ ID NO: 1 is tabulated in Table 1, it cannot be determined whether or not the "gene" is differentially expressed in colorectal tumors, or whether or not the "gene" is expressed in normal colon and rectal tissues, and other tissues, such bone marrow and lung, where one might expect to find metastases of colorectal tumors. If the nucleic acid molecule of SEQ ID NO: 1 is not differentially expressed in colorectal tumors relative to normal colon and rectal tissues, the claimed invention is not expected to have a "real-world" utility. Unless the nucleic acid molecule is differentially expressed in colorectal cancer relative to normal colorectal tissue, and until it is determined whether the nucleic acid molecule is significantly over- or under-expressed, and finally until it is determined if such differential expression is correlated with the presence of colorectal cancer in patients, the claimed invention cannot be used in a manner that might immediately benefit the public, as further experimentation would need be performed before the invention could be practiced in a clinical setting to diagnostically assess whether a patient has colorectal cancer, in which case the claimed invention does not now have a "real-world" utility as required by 35 USC § 101.

The existing information disclosed by Applicant's application would merely provide the artisan with an invitation to perform further investigation, which might ultimately lead to a derivation of a specific benefit, or which might not; and in either case, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to allow the artisan to use the disclosure in the manner asserted to provide an immediate benefit to the public. To fulfill the requirements of 35 USC § 101, the skilled artisan must be able to use a claimed invention in the manner asserted by Applicant's to provide some immediate benefit to the public.

Before the claimed method could be used to benefit the public, the practitioner would need to determine if the nucleic acid molecule of SEQ ID NO: 1 is differentially expressed in colorectal cancer relative to normal colorectal tissues and if so, how so and to what extent.

The teachings of Rae et al. (*International Journal of Cancer* **88**: 726-732, 2000) emphasize the lack of correlation between an initially observed differential expression of a gene or gene product and its use as a biomarker. Rae et al. teach a highly sensitive method for determining the differential expression of genes associated with renal cell carcinoma (RCC) (abstract). A total of sixteen tumor and sixteen adjacent normal tissue samples were collected at the same time from the patients. The tumor tissue was histologically confirmed to be clear-cell RCC; and the tumors were staged by a conventional system. Rae et al. discloses that using differential display PCR, some genes were identified that are expressed at higher levels in the tumor specimens than in the normal specimens, while other genes were expressed at lower levels in the tumor specimens. Notably, Rae et al. had planned to use as a positive control, primers that amplify a cDNA encoding DD96, a gene that had been previously reported by Kocher et al. to be up regulated in RCC. However, Rae et al. found in contrast to the results reported by Kocher et al., no *consistent* up- or down-regulation of *DD96* was evident when using either RT-PCR or Northern analysis and conclude, "we do not believe that *DD96* up-regulation is highly associated with RCC, particularly in early progression, and does not warrant extensive further investigation in the context of this disease" (page 731, column 2). Rae et al. suggest that the results of Kocher et al. were inaccurate because their experiments were not properly controlled. In contrast to the study of Kocher et al., Rae et al. disclose, "only those cDNAs clearly up- or down-regulated in duplicate paired RCC and normal kidney samples (Fig. 1) from 4 different patients were considered to be definitively differentially expressed" (page 728, column 1). Moreover, their results were considered accurate only when the cDNAs were successfully re-amplified and only when no expression was detected in the paired sample. Applicant's disclosure does not teach that matched tumor and normal tissue specimens were used to prepare the material that was used in the analysis of differential expression.

Regarding the possibility that the claimed invention might be used to assess whether a patient is afflicted with colorectal cancer, Ward (*Developmental Oncology* 1985; **21**: 91-106) teaches not all markers can be reliably used in primary diagnosis. Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable. Rather, Ward teaches some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease. Thus, even if data were presented showing that the nucleic acid molecule of SEQ ID NO: 1 is abnormally expressed in colorectal cancer, such data would not be immediately useful, or indicative that the differential expression of the "CBF9 gene" can be used to diagnose colorectal cancer. Critchfield (*Disease Markers* **15**: 108-111, 1999) teaches: "Indeed, to truly benefit society, the clinical value of the gene must be established" (page 109, column 1). Following the discovery of a novel gene Critchfield discusses the lengthy process that is involved in determining its usefulness as a biomarker for diagnosis; and in view of Critchfield, given only the benefit of Applicant's present disclosure of the invention, it is apparent the skilled artisan could not immediately utilize the claimed invention in a manner that might benefit the public.

In summary, the instant claims are drawn to a method for diagnosing colorectal cancer comprising determining and comparing the levels of expression of the nucleic acid molecule of SEQ ID NO: 1, the expression or activity of which, as yet, bears no established association with the incidence or recurrence of colorectal cancer. Until some actual and specific significance can be attributed to expression or activity of the nucleic acid molecule of SEQ ID NO: 1, the inventive process has not been refined or developed to a point where a specific benefit can be derived by the public from the granting of a patent upon the Applicant's application. In the absence of any established clinical significance to the expression, or lack thereof, of the nucleic acid molecule of SEQ ID NO: 1 or any other nucleic acid molecule, which is at least 90% identical thereto, or its relative abundance or insufficiency, there is no immediately obvious "patentable" use for the claimed invention. To employ the disclosure of the novel nucleic acid molecule of SEQ ID NO: 1 in the diagnosis, or assessment of the presence or recurrence of colorectal cancer, as is the asserted utility of the claimed invention,

would require further research, which should be regarded as constituting part of the inventive process. Because the specification does not disclose a currently available, "real world" use for the claimed invention, the requirements set forth under 35 U.S.C. § 101 have not been met.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 32-44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth in section 10 above, one skilled in the art clearly would not know how to use the claimed invention.

15. If the grounds of rejection of the claims under 35 USC §§ 101 and 112, first paragraph for the reasons set forth in sections 10 and 12, respectively, were to be obviated, claims 32-44 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the methods of claims 32-44, wherein said method comprises determining the expression of a nucleic acid molecule comprising SEQ ID NO: 1, does not reasonably provide enablement for practicing the methods of claims 32-44, as presently claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein is insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention without need to perform additional, undue experimentation.

The factors that have been considered in determining that undue experimentation would be required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Even if one were enabled to use the claimed method comprising determining the expression of a nucleic acid molecule comprising SEQ ID NO: 1 to diagnose colorectal cancer, the skilled artisan cannot predict whether any "gene", even one that is at least 90% identical to a diagnostically useful biomarker, will be useful as a biomarker, because the skilled artisan cannot predict whether the expression or activity of such a gene will be associated with the incidence of colorectal cancer. Skolnick et al. (*Trends in Biotechnology* **18**: 34-39, 2000) teaches that assigning functional activities for any particular protein or protein family based upon sequence homology alone is inaccurate; the fact that another nucleic acid molecule comprises a polynucleotide sequence that is similar to the polynucleotide sequence set forth in SEQ ID NO: 1 cannot be construed as evidence that the other nucleic acid molecule can be used as a biomarker to assess whether a patient is afflicted with colorectal cancer, since Skolnick et al. teaches, even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein; and it follows that any association of the expression of the other nucleic acid molecule and the presence of colorectal cancer can only be determined empirically.

16. Claims 32-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are interpreted to encompass a method comprising determining the expression of a genus of "genes" having a polynucleotide sequence that is "at least 90% identical" to SEQ ID NO: 1.

The disclosure includes only an adequate description of a nucleic acid molecule having the polynucleotide sequence set forth in SEQ ID NO: 1.

At page 19, paragraph 63, the specification discloses the term "gene" includes nucleic acid molecules, which are fragments of larger genes and can comprise coding regions, non-coding regions, and mixtures of coding and non-coding regions.

The structure of a gene cannot be instantly envisioned or predicted, even given a description of an mRNA molecule encoded by the gene, or of a cDNA molecule derived therefrom. A gene contains introns, or intervening sequences that are dispersed among the exons encoding the transcription and translation products of the gene. Introns do not provide coding information that is utilized in producing the RNA transcript or polypeptide encoded by a gene, and the polynucleotide sequences of the introns are excised during maturation of the RNA transcript, or mRNA so that only the polynucleotide sequences of the spliced exons remain. Therefore, the artisan cannot deduce the structure of an intron, or of a gene containing an intron given only the polynucleotide sequence of an mRNA molecule, or cDNA derived therefrom. In addition, a gene comprises polynucleotide sequences at either end, i.e., the 5' and 3' ends, which contains regulatory information. For example, the promoter of the gene is most commonly positioned at the 5' end of the gene and regulates the transcription of the gene. Because the polynucleotide sequence of the promoter of a gene is not transcribed, its structure cannot be surmised given only the polynucleotide sequence of the RNA transcript of the gene. Other regulatory sequences are positioned at the 5' and

3' ends of the gene, which encode portions of the RNA transcript, which are not translated.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The specification does not include an adequate written description of any one member of the genus of genes to which the claims refer, because the specification does not set forth a detailed description of any one gene, including the polynucleotide sequences of the introns, the boundaries of the introns and exons, and the 5' and 3' regulatory sequences, such as the promoter.

In the absence of a detailed description of at least a substantial or representative number of members of the genus of genes having at least 90% identity to SEQ ID NO: 1 to which the claims refer, including the polynucleotide sequences of the introns, the boundaries of the introns and exons, and the 5' and 3' regulatory sequences, such as the promoter, one skilled in the art would not reasonably conclude that Applicants had possession of the claimed invention at the time the application was filed.

Furthermore, *The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement* (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including

description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims not only encompass genes but also encompass a genus of variant species of polynucleotide, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus, such as a correlation between structure and function, or a combination thereof.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Skolnick, et al (*Trends in Biotechnology* **18**: 34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in polynucleotide or amino acid sequence, that a variant of the "gene" of SEQ ID NO: 2 will be associated with the incidence of colorectal cancer, or have the same or similar biologic function as a protein encoded by SEQ ID NO: 1. Therefore, as evidenced by the teachings of Skolnick, et al, the art is unpredictable.

In accordance with the *Guidelines*, because the art is unpredictable, SEQ ID NO: 1 is not representative of the genus of genes, as a whole, to which the claims refer. Factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete. As only the structure of SEQ ID NO: 1 is adequately described, the specification does not include an adequate description of at least a representative number of members of the genus of genes to which the claims refer. Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed, because the specification does not disclose a correlation between the recited common structural feature of the members of the genus of genes to which the claims refer, i.e., having a polynucleotide sequence that is at least 90% identical to SEQ ID NO: 1, and any particular function. Accordingly, the written description of the claimed invention would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
January 15, 2004

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600